

This listing of claims will replace all prior versions, and listings, of claims in the application.

Listing of Claims:

1-38. (Canceled)

39. (Currently Amended) A gene-targeted ~~rodent~~ mouse heterozygous for a human Familial Alzheimer's Disease (FAD) mutation comprising a human mutation of the presenilin-1 (PS-1 gene), and a human transgene for Swedish APP695, wherein the A β 42 protein level is elevated relative to the A β 42 protein level in a wild-type ~~rodent~~ mouse.

40. (Currently Amended) A gene-targeted ~~rodent~~ mouse homozygous for a human Familial Alzheimer's Disease (FAD) mutation comprising a human mutation of the presenilin-1 (PS-1 gene), and a human transgene for Swedish APP695, wherein the A β 42 protein level is elevated relative to the A β 42 protein level in a wild-type ~~rodent~~ mouse.

41. (Currently Amended) The ~~rodent~~ mouse of claim 39 wherein said mutation of said PS-1 gene is P264L.

42. (Currently Amended) The ~~rodent~~ mouse of claim 40 wherein said mutation of said PS-1 gene is P264L.

43-46. (Canceled)

47. (Currently Amended) Generational offspring of the ~~rodent~~ mouse of claim 39 wherein said mutant PS-1 gene is expressed.

48. (Currently Amended) Generational offspring of the ~~rodent~~ mouse of claim 40 wherein said mutant PS-1 gene is expressed.

49. (Currently Amended) A method for screening chemical compounds for the ability to decrease *in vivo* levels of the A β peptide, said method comprising the steps of:

a) administering said chemical compound to the ~~rodent~~ mouse of claim 39; and

b) measuring the amount of A β peptide in a tissue sample from said ~~rodent~~ mouse, wherein a decrease in the amount of A β peptide in said tissue sample is indicative of a chemical compound that has the ability to decrease *in vivo* levels of said A β peptide.

50. (Currently Amended) A method for screening chemical compounds for the ability to decrease *in vivo* levels of the A β peptide, said method comprising the steps of:

a) administering said chemical compound to the ~~rodent~~ mouse of claim 40; and

b) measuring the amount of A β peptide in a tissue sample from said ~~rodent~~ mouse, wherein a decrease in the amount of A β peptide in said tissue sample is indicative of a chemical compound that has the ability to decrease *in vivo* levels of said A β peptide.

51. (Currently Amended) A method for screening chemical compounds for the ability to decrease *in vivo* levels of the A β peptide, said method comprising the steps of:

a) administering said chemical compound to the ~~rodent~~ mouse of claim 47; and

b) measuring the amount of A β peptide in a tissue sample from said ~~rodent~~ mouse, wherein a decrease in the amount of A β peptide in said tissue sample is indicative of a chemical compound that has the ability to decrease *in vivo* levels of said A β peptide.

52. (Currently Amended) A method for screening chemical compounds for the ability to decrease *in vivo* levels of the A β peptide, said method comprising the steps of:

a) administering said chemical compound to the ~~rodent~~ mouse of claim 48; and

b) measuring the amount of A β peptide in a tissue sample from said ~~rodent~~ mouse, wherein a decrease in the amount of A β peptide in said tissue sample is indicative of a chemical compound that has the ability to decrease *in vivo* levels of said A β peptide.

53. (Original) The method of claim 49 wherein said tissue sample is selected from the group consisting of brain tissue, non-brain tissue and body fluids.

54. (Original) The method of claim 50 wherein said tissue sample is selected from the group consisting of brain tissue, non-brain tissue and body fluids.
55. (Original) The method of claim 51 wherein said tissue sample is selected from the group consisting of brain tissue, non-brain tissue and body fluids.
56. (Original) The method of claim 52 wherein said tissue sample is selected from the group consisting of brain tissue, non-brain tissue and body fluids.
57. (Currently Amended) A method for identifying a compound for treating Alzheimer's disease comprising the steps of:
- a) administering a compound to the ~~rodent~~ mouse of claim 39; and
 - b) measuring the amount of A β peptide in a tissue sample from said ~~rodent~~ mouse,
- wherein a decrease in the amount of A β peptide in said tissue sample is indicative of a compound that can be used to treat Alzheimer's disease.
58. (Currently Amended) A method for identifying a compound for treating Alzheimer's disease comprising the steps of:
- a) administering a compound to the ~~rodent~~ mouse of claim 40; and
 - b) measuring the amount of A β peptide in a tissue sample from said ~~rodent~~ mouse,
- wherein a decrease in the amount of A β peptide in said tissue sample is indicative of a compound that can be used to treat Alzheimer's disease.
59. (Currently Amended) A method for identifying a compound for treating Alzheimer's disease comprising the steps of:
- a) administering a compound to the ~~rodent~~ mouse of claim 47; and

b) measuring the amount of A β peptide in a tissue sample from said ~~rodent~~ mouse, wherein a decrease in the amount of A β peptide in said tissue sample is indicative of a compound that can be used to treat Alzheimer's disease.

60. (Currently Amended) A method for identifying a compound for treating Alzheimer's disease comprising the steps of:

a) administering a compound to the ~~rodent~~ mouse of claim 48; and

b) measuring the amount of A β peptide in a tissue sample from said ~~rodent~~ mouse, wherein a decrease in the amount of A β peptide in said tissue sample is indicative of a compound that can be used to treat Alzheimer's disease.

61. (Original) The method of claim 57 wherein said tissue sample is selected from the group consisting of brain tissue, non-brain tissue and body fluids.

62. (Original) The method of claim 58 wherein said tissue sample is selected from the group consisting of brain tissue, non-brain tissue and body fluids.

63. (Original) The method of claim 59 wherein said tissue sample is selected from the group consisting of brain tissue, non-brain tissue and body fluids.

64. (Original) The method of claim 60 wherein said tissue sample is selected from the group consisting of brain tissue, non-brain tissue and body fluids.

65-76. (Canceled)

77. (Currently Amended) A gene-targeted ~~rodent~~ mouse heterozygous for a human presenilin-1 (PS-1) mutation and comprising a human Swedish mutation, said ~~rodent~~ mouse comprising in its genome:

a DNA sequence encoding a PS-1 protein comprising the human P264L mutation; and

a DNA sequence encoding a human amyloid precursor protein having the Swedish APP695 mutation;

wherein the A β 42 protein level is elevated relative to the A β 42 protein level in a wild-type ~~rodent~~ mouse.

78. (Canceled)

79. (Currently Amended) The ~~rodent~~ mouse of claim 77 wherein codon 264 of the PS-1 gene is changed from CCG to CTT, CTC, CTA, CTG, TTA, or TTG.

80. (Currently Amended) The ~~rodent~~ mouse of claim 79 wherein codon 264 of the PS-1 gene is changed from CCG to CTT.

81. (Currently Amended) The ~~rodent~~ mouse of claim 77 wherein codon 265 of the PS-1 gene is changed from AAA to AAG.

82. (Currently Amended) A generational offspring of the ~~rodent~~ mouse of claim 77 wherein said offspring comprises in its genome:

a DNA sequence encoding a PS-1 protein comprising the human P264L mutation; and

a DNA sequence encoding a human amyloid precursor protein having the Swedish APP695 mutation;

wherein the A β 42 protein level is elevated relative to the A β 42 protein level in a wild-type ~~rodent~~ mouse.

83. (Currently Amended) A gene-targeted ~~rodent~~ mouse homozygous for a human presenilin-1 (PS-1) mutation and comprising a human Swedish mutation, said ~~rodent~~ mouse comprising in its genome:

a DNA sequence encoding a PS-1 protein comprising the human P264L mutation; and

a DNA sequence encoding a human amyloid precursor protein having the Swedish APP695 mutation;

wherein the A β 42 protein level is elevated relative to the A β 42 protein level in a wild-type ~~rodent~~ mouse.

84. (Canceled)

85. (Currently Amended) The ~~rodent~~ mouse of claim 83 wherein codon 264 of the PS-1 gene is changed from CCG to CTT, CTC, CTA, CTG, TTA, or TTG

86. (Currently Amended) The ~~rodent~~ mouse of claim 85 wherein codon 264 of the PS-1 gene is changed from CCG to CTT.

87. (Currently Amended) The ~~rodent~~ mouse of claim 83 wherein codon 265 of the PS-1 gene is changed from AAA to AAG.

88. (Currently Amended) A generational offspring of the ~~rodent~~ mouse of claim 83 wherein said offspring comprises in its genome:

a DNA sequence encoding a PS-1 protein comprising the human P264L mutation; and

a DNA sequence encoding a human amyloid precursor protein having the Swedish APP695 mutation;

wherein the A β 42 protein level is elevated relative to the A β 42 protein level in a wild-type ~~rodent~~ mouse.

89. (Currently Amended) A method for screening a compound for the ability to decrease *in vivo* levels of the A β peptide comprising the steps of:

administering said compound to the ~~rodent~~ mouse of claim 77; and

measuring the amount of A β peptide in a tissue sample from said ~~rodent~~ mouse;

wherein a decrease in the amount of A β peptide in said tissue sample is indicative of a compound that has the ability to decrease *in vivo* levels of said A β peptide.

90. (Currently Amended) A method for screening a compound for the ability to decrease *in vivo* levels of the A β peptide comprising the steps of:

administering said compound to the ~~rodent~~ mouse of claim 82; and

measuring the amount of A β peptide in a tissue sample from said ~~rodent~~ mouse;

wherein a decrease in the amount of A β peptide in said tissue sample is indicative of a compound that has the ability to decrease *in vivo* levels of said A β peptide.

91. (Currently Amended) A method for screening a compound for the ability to decrease *in vivo* levels of the A β peptide comprising the steps of:

administering said compound to the ~~rodent~~ mouse of claim 83; and

measuring the amount of A β peptide in a tissue sample from said ~~rodent~~ mouse;

wherein a decrease in the amount of A β peptide in said tissue sample is indicative of a compound that has the ability to decrease *in vivo* levels of said A β peptide.

92. (Currently Amended) A method for screening a compound for the ability to decrease *in vivo* levels of the A β peptide comprising the steps of:

administering said compound to the ~~rodent~~ mouse of claim 88; and

measuring the amount of A β peptide in a tissue sample from said ~~rodent~~ mouse;

wherein a decrease in the amount of A β peptide in said tissue sample is indicative of a compound that has the ability to decrease *in vivo* levels of said A β peptide.

93. (Previously Presented) The method of claim 89 wherein said tissue sample is brain tissue, non-brain tissue, or a body fluid.

94. (Previously Presented) The method of claim 90 wherein said tissue sample is brain tissue, non-brain tissue, or a body fluid.
95. (Previously Presented) The method of claim 91 wherein said tissue sample is brain tissue, non-brain tissue, or a body fluid.
96. (Previously Presented) The method of claim 92 wherein said tissue sample is brain tissue, non-brain tissue, or a body fluid.
97. (Currently Amended) The ~~rodent~~ mouse of claim 39 wherein said human mutation of the PS-1 gene is A79V, V82L, V96F, Y115C, E120D, E120K, M139I, M139T, M139V, I143F, I143T, M146I, M146L (A \Rightarrow T), H163Y, G209V, A231T, A231V, M233T, L235P, L250S, A260V, L262F, C263R, P264L, P267S, R269H, R278T, E280A, E280G, A285V, E318G, G378E, G384A, L392V, M146L (A \Rightarrow C), M146V, H163R, I213T, L286V, A246E, Y115H, T116N, P117L, L171P, E123L, N135D, C410Y, A426P, P436S, M139K, T147I, W165C, L173W, S390I, L166R, S169L, P436Q, S169P, E184D, G209R, L219P, M233L, A409T, E273A, L282R, G378A, N405S, A409T, L424R, a Δ exon 9 splice acceptor site deletion mutation (G \Rightarrow T with S290C), a Δ exon 9 splice acceptor site deletion mutation (G \Rightarrow A with S290C), a Δ exon 9 Finn 4,555 basepair deletion, a Δ intron 4 splice donor consensus sequence G deletion, a C \Rightarrow T mutation at position -48 in the 5' promoter, a C \Rightarrow G mutation at position -280 in the 5' promoter, or a A \Rightarrow G mutation at position -2818 in the 5' promoter.
98. (Currently Amended) The ~~rodent~~ mouse of claim 40 wherein said human mutation of the PS-1 gene is A79V, V82L, V96F, Y115C, E120D, E120K, M139I, M139T, M139V, I143F, I143T, M146I, M146L (A \Rightarrow T), H163Y, G209V, A231T, A231V, M233T, L235P, L250S, A260V, L262F, C263R, P264L, P267S, R269H, R278T, E280A, E280G, A285V,

DOCKET NO.: CEPH-1066
Application No.: 09/621,897
Office Action Dated: June 6, 2003

PATENT
REPLY FILED UNDER EXPEDITED
PROCEDURE PURSUANT TO
37 CFR § 1.116

E318G, G378E, G384A, L392V, M146L (A⇒C), M146V, H163R, I213T, L286V, A246E, Y115H, T116N, P117L, L171P, E123L, N135D, C410Y, A426P, P436S, M139K, T147I, W165C, L173W, S390I, L166R, S169L, P436Q, S169P, E184D, G209R, L219P, M233L, A409T, E273A, L282R, G378A, N405S, A409T, L424R, a Δ exon 9 splice acceptor site deletion mutation (G⇒T with S290C), a Δ exon 9 splice acceptor site deletion mutation (G⇒A with S290C), a Δ exon 9 Finn 4,555 basepair deletion, a Δ intron 4 splice donor consensus sequence G deletion, a C⇒T mutation at position -48 in the 5' promoter, a C⇒G mutation at position -280 in the 5' promoter, or a A⇒G mutation at position -2818 in the 5' promoter.